Thyroid Cancer Rates and ^{131}I Doses From Nevada Atmospheric Nuclear Bomb Tests

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Background: **We examined data on death from thyroid cancer across the continental United States and data on incidence from selected areas of the country for evidence of an association between this disease and exposure to radioactive iodine (^{131}I) from nuclear tests in Nevada in the 1950s.** ***Methods:*** **Analyses involving 4602 thyroid cancer deaths (1957–1994) and 12 657 incident cases of thyroid cancer (1973–1994) were performed. Excess relative risks (ERRs) per Gray (Gy) of radiation were estimated by relating age-, calendar year-, sex-, and county-specific rates to estimates of dose to the thyroid that take age at exposure into account.** ***Results:*** **Analyses of cumulative dose yielded negative ERRs that were not statistically significant. An association was suggested for dose received by children under 1 year of age for both mortality data (ERR per Gy = 10.6; 95% confidence interval [CI] = –1.1 to 29) and incidence data (ERR per Gy = 2.4; 95% CI = –0.5 to 5.6); no association was found for dose received at older ages. For mortality data, but not incidence data, there was an elevated ERR in the 1950–1959 birth cohort of 12.0 (95% CI = 2.8 to 31) per Gy.** ***Conclusions:*** **Risk of thyroid cancer from exposure to ^{131}I from atmospheric nuclear tests did not increase with cumulative dose or dose received at ages 1–15 years, but associations were suggested for individuals exposed under 1 year of age and for those in the 1950–1959 birth cohort. The absence of increased risk from dose received at ages 1–15 years is not consistent with studies of children exposed to external radiation sources. This inconsistency may result from the limitations and biases inherent in ecologic studies, including the error introduced when studying a mobile population. These problems preclude making a quantitative estimate of risk due to exposure; however, given such limitations, it is perhaps remarkable that any evidence of the effects of ^{131}I emerges from this study. [J Natl Cancer Inst 1998;90:1654–60]**

A recent report by the National Cancer Institute (NCI) *(1)* provides estimates of ^{131}I doses to the thyroid resulting from exposure from atmospheric nuclear tests conducted at the Nevada test site for representative categories of individuals residing in each county in the continental United States. These tests released an estimated 6 exabecquerels (150 million curies) of ^{131}I in the atmosphere, primarily in the years 1952, 1953, 1955, and 1957. On the basis of evidence from studies of persons exposed to external radiation, excess thyroid cancers would be expected, with most occurring in persons who were children during the period of exposure, since both thyroid cancer risks and thyroid doses are estimated to be much larger for exposures in childhood than in adulthood *(2)*. Because direct data on the effects of exposure to ^{131}I are limited, the magnitude of the excess is highly uncertain.

In this report, available data on U.S. thyroid cancer mortality and incidence are examined for evidence that thyroid cancers occurred as a result of ^{131}I exposure from atmospheric nuclear tests conducted in Nevada. This examination was accomplished by determining whether county- and state-specific thyroid mortality and incidence rates are related to county- and state-specific dose estimates and by determining whether evidence of an association is strongest among those who were children during the period of exposure.

Materials and Methods

Dosimetry Data

In the NCI report *(1)*, thyroid doses were estimated for each of the 90 nuclear weapons tests conducted at the Nevada test site that gave rise to substantial offsite contamination by radioactive materials. Estimates of mean thyroid dose are given, county by county, for 14 age and sex categories (four *in utero* categories; four categories for infants under 1 year of age; single categories for 1–4 years of age, 5–9 years of age, 10–14 years of age, and 15–19 years of age; and adult males and adult females), and for four sets of assumptions about milk consumption. The major contributor to the thyroid dose for most individuals is the consumption of fresh cow's milk contaminated with ^{131}I. In addition, thyroid doses from inhalation of air contaminated with ^{131}I and from the consumption of foodstuffs other than fresh cow's milk are included. The estimated thyroid doses were derived from available measurements of fallout, with extensive use of environmental transfer mathematical models, and these estimates are subject to large uncertainties. Doses depend strongly on environmental factors (occurrence of fallout in the presence or absence of precipitation, availability of pasture greens, and dairy practices regarding cattle feed) as well as human factors (geographic location at the time of fallout, age, and consumption rates of fresh milk). Because the thyroids of young children are much smaller than those of adults and because their consumption of fresh cow's milk is usually greater than that of adults, the estimated thyroid doses received by young children are about an order of magnitude greater than those received by adults in the same geographic location.

Analyses in this report utilize estimates of dose to the thyroid received from test series conducted in seven time periods for all counties of the contiguous United States, for seven age-at-exposure categories (doses were averaged over the four periods *in utero* and over the four periods under 1 year of age), and for the two sexes (separate estimates available only for adults). Doses are based on the assumption of average milk consumption scenarios. The approach used for estimating thyroid doses took uncertainties from several sources into account and provided a lognormal distribution for any given estimate. Our analyses were based on the means of these distributions, although repeat analyses based on medians were also performed and led to similar conclusions. The overall U.S. averages for the respective periods 1951, 1952, 1953, 1955, 1957, 1958, and 1961+ were 0.0 cGy, 0.7 cGy, 0.6 cGy, 0.2 cGy, 0.8 cGy, 0.0 cGy, and 0.1 cGy, respectively, totaling 2.4 cGy. The estimated doses depend strongly on age at exposure with average U.S. doses of 4.3 cGy, 12.6 cGy, 10.0 cGy, 6.7 cGy, 4.4 cGy, 3.1 cGy, and 1.1 cGy for the seven respective age-at-exposure categories (i.e., *in utero*, 0 to <1 year, 1–4 years, 5–9 years, 10–14 years, 15–19 years, and ≥20 years of age).

Thyroid Cancer Mortality and Incidence Data

Data on deaths with thyroid cancer as the underlying cause, classified by sex, single calendar year (1957–1994), and 5-year age-at-risk group (ages 5–54 years) were provided for 3053 U.S. counties (excluding Hawaii and Alaska) by the National Center for Health Statistics, Hyattsville, MD. Data on similarly classified mid-year population estimates, based on data from the U.S. Bureau of the Census, were used to form person-years at risk. Calendar years before 1957 and the 0- to 4-year age-at-risk group were not used because radiation-induced thyroid

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cancers have usually been found to have a minimal latent period of 4 or 5 years. To keep the size of the data file to a manageable level, the older age groups (55 years old or older) were not used; persons whose follow-up was limited by this restriction would have been at least 13 years old in 1952 when the first nuclear test contributing substantially to dose was conducted. Data on thyroid cancer incidence were available by single calendar years (1973–1994) and 5-year age groups for 194 counties covered by eight Surveillance, Epidemiology, and End Results (SEER)[1] tumor registries (Atlanta, Connecticut, Detroit, Iowa, New Mexico, San Francisco, Seattle, and Utah). The average dose for the 194 counties included in the incidence analyses was 2.5 cGy, slightly higher than the average dose of 2.4 cGy for all 3053 counties.

Statistical Methods

A dose was assigned to each category defined by county, sex, calendar year (y), and 5-year age-at-risk group (a to $a + 4$). This was done by first calculating the county- and sex-specific doses that would have been received by subjects born at the beginning of each of the calendar years in the period of interest, taking into account the age at exposure at the time of each of the seven test series. For these calculations, the entire dose for the period 1961+ was assigned to 1962, the year when most of it was received. Next, the dose for the beginning of the birth year, $y - a$, was assigned to the age–calendar year combination a and y. Approximately half the subjects contributing person-years to such a category would have been born in the year $y - a$, and the other half would have been born in the year $y - a - 1$; thus, the beginning of the year, $y - a$, seems a reasonable estimate of the average time of birth. Finally, the dose assigned to calendar year, y, and 5-year age group, a to $a + 4$, was calculated as the average of the doses for the five contributing single years of age, which would be the doses for persons born at the beginning of the birth years $y - a - 4$ through $y - a$. For example, the category with ages 15–19 years ($a = 15$) and calendar year 1970 ($y = 1970$) would include contributions from persons born at the beginning of the 5 years 1951–1955. To allow for a minimal latent period of 5 years, doses received in the 5 years preceding the time at risk were not included. The dose assignment is necessarily based on the assumption that subjects resided in the same county from 1951 (or the year of first exposure for subjects born after 1951) to the end of their follow-up.

Data were then collapsed (across counties) into the following cumulative dose categories (in cGy): 0, >0 to <0.1, 0.1 to <0.2, 0.2 to <0.5, 0.5 to <1, 1 to <1.5, 1.5 to <2, 2 to <3, 3 to <4, 4 to <6, 6 to <9, 9 to <12, 12 to <16, 16 to <24, 24 to <36, 36 to <48, 48 to <64, and ≥64. Also presented are results of analyses based on mortality rates and average doses for states (weighted by the county population size) rather than for counties. The rationale for these analyses is that the estimated doses for states might be less uncertain than those for counties and that migration between states would be less frequent than that between counties.

Statistical analyses used Poisson regression methods, where it is assumed that the number of thyroid cancer deaths or cases in each cell is a Poisson variable with the mean given by the product of the person-years and a thyroid cancer mortality or incidence rate for the cell. These analyses were implemented by use of the AMFIT module of the software package EPICURE *(3)*. All P values reported are two-sided.

Dose–response analyses were based on the linear relative risk model in which the cancer risk is given by

$$\lambda_j [1 + \beta z],$$

where j indexes strata defined by age (5-year categories), calendar year (single years), and sex; λ_j is the rate in unexposed individuals; β is the excess relative risk per Gy; and z is the dose in Gy. The linear relative risk model has been used extensively in analyzing epidemiologic data on radiation risks, including risks of thyroid cancer *(4,5)*. Confidence intervals (CIs) and tests of the null hypothesis that $\beta = 0$ were based on the likelihood ratio statistic. Large negative values of β can lead to negative relative risks; for this reason, lower confidence limits do not always exist, and, in these cases, the lower confidence limits are reported as <0.

With the approach described above, dose–response analyses compare thyroid cancer rates in counties with high doses to those in counties with lower doses, with strata including subjects with the highest doses (because they were young during the period of exposure) making the strongest contribution. Strata with mainly birth years of subjects who were older during the period of exposure or birth years after the last nuclear test have little exposure and contribute minimally to the dose–response analysis, whereas strata including birth years of subjects who were young during the period of exposure have much higher exposures and greater exposure variability and contribute much more substantially to the dose–response analysis.

Although the dose assignment method takes into account the dependence of dose on age at exposure, it does not account for the substantial evidence that thyroid cancer risks decrease with increasing age at exposure. One approach to account for this decrease was to calculate a risk-weighted dose by multiplying the age-specific county doses by the estimated age-specific excess relative risk (ERR) per Gy, obtained from a pooled analyses of data from five cohort studies of thyroid cancer risks in persons exposed to external radiation *(4)*. These ERRs were 9.8, 9.8, 4.9, 2.5, 1.25, and 0 per Gy for the respective exposure ages of less than 1 year, 1–4 years, 5–9 years, 10–14 years, 15–19 years, and 20 or more years. Categories for the risk-weighted doses were those used for dose but with the cut points divided by 10. Because there is substantial uncertainty in the age-specific ERRs and their applicability to ^{131}I exposure, age dependence was also examined by conducting analyses of doses received at specific ages. These age-specific analyses weight the contributions of various birth years differently than do analyses based on the total dose. For example, analyses of dose received under 1 year of age weight heavily the contributions from age–calendar year combinations that include the birth years 1952, 1953, 1955, and 1957 and give no weight to combinations that do not include any of the birth years from 1951 to 1963.

Risks were also evaluated for categories defined by birth year. Mortality and incidence rates are most commonly presented by 5-year categories of age (0–4, 5–9, . . .) and calendar year (1950–1954, 1955–1959, . . .), and birth cohorts can be defined by diagonal arrays of these combinations. For example, the array with categories of ages 5–9 years in 1960–1964, ages 10–14 years in 1965–1969, ages 15–19 years in 1970–1974, etc., includes persons born in the 10-year period 1950–1959. Each birth cohort is designated by its central birth year, 1955 in the example. For analyses in this report, the birth cohorts evaluated separately were 1940 or earlier, 1945, 1950, 1955, and 1960 or later. Preliminary age–period–cohort analyses (results not shown) had suggested evidence of increased risk only in the 1950 and 1955 cohorts.

In addition to the analyses in which dose was treated as a continuous variable, dose (and risk-weighted dose) categories were defined to correspond roughly to the 50th and 75th percentiles of the distributions of person-years for the combined 1945, 1950, and 1955 birth cohorts; these strata contribute most of the higher dose person-years and deaths. Relative risks were then calculated by use of the lowest category as the baseline. CIs were based on the asymptotic standard error of the logarithms of the estimated relative risks.

Results

Table 1 shows the distribution of person-years, thyroid cancer deaths, and thyroid cancer cases by dose category. The mortality data include about 18 times more person-years than the incidence data; however, because thyroid cancer is rarely fatal, there are nearly three times as many cases as deaths.

Table 2 shows results of dose–response analyses, with mortality data presented for both county- and state-specific doses. For comparability with high-dose studies, estimates are presented per Gy even though none of the doses in this study were as high as 1 Gy. These results provide little indication that thyroid cancer risk increases with increasing exposure level.

Results of analyses of doses received at specific ages are shown in Table 3. When only dose received under age 1 year was included (analysis A in Table 3), positive ERRs were observed for all three analyses, with P values ranging from .054 to .11. Detailed examination of the data revealed that the mortality analyses based on county-specific doses were strongly influenced by two deaths with doses under age 1 year exceeding 9 cGy (these deaths occurred in Broadwater County, MT, and Washington County, UT); without the 9+ cGy data, the estimated ERR was reduced from 10.6 to 6.5 per Gy, and the P value changed from .085 to .34. The incidence results were strongly influenced by nine cases with doses under age 1 year exceeding 9 cGy, all of which occurred in

Table 1. Distribution of person-years, thyroid cancer deaths, and thyroid cancer cases by ^{131}I dose category

Cumulative dose, cGy	Mortality data: County-specific doses* No. of person-years, $\times 10^{-6}$	Mortality data: County-specific doses* No. of deaths	Mortality data: State-specific doses* No. of person-years, $\times 10^{-6}$	Mortality data: State-specific doses* No. of deaths	Incidence data: county-specific doses* No. of person-years, $\times 10^{-6}$	Incidence data: county-specific doses* No. of cases
0	1031.6	57	917.3	43	88.9	1350
>0 to <1	1395.9	2108	1305.4	1721	58.9	2978
≥1 to <2	694.9	1154	796.0	1588	32.0	2019
≥2 to <4	742.7	688	721.7	643	36.7	2262
≥4 to <6	461.6	268	537.4	267	17.7	1180
≥6 to <9	369.0	200	393.1	207	20.6	1273
≥9 to <12	175.5	71	223.3	94	13.3	814
≥12 to <24	139.7	54	119.2	37	12.7	749
≥24	5.6	2	2.8	2	0.6	32
Total	5016.3†	4602	5016.3†	4602	281.5†	12 657

*Dose category is determined by year of birth as well as county or state; thus, age varies markedly by these categories. For example, the 0-dose category is made up entirely of persons born in 1964 or later, and the higher dose categories are made up of persons born in the early and mid-1950s.

†The total numbers of person-years differ slightly from the sums of the cumulative dose categories because of rounding.

Table 2. Estimates of the excess relative risk (ERR) per Gray (Gy)* of ^{131}I dose, the ERR per unit of risk predicted from studies of external exposure, and relative risks by category

	Mortality data: County-specific doses	Mortality data: State-specific doses	Incidence data: county-specific doses
ERR per Gy (95% CI)†	−0.6 (<0 to 0.9)	−0.1 (−1.6 to 1.7)	−0.4 (−0.8 to 0.1)
P‡	.44	.91	.12
Relative risks by categories of dose (95% CI)†			
0–3.99 cGy§	1.00	1.00	1.00
4–8.99 cGy	0.96 (0.85 to 1.08)	0.93 (0.82 to 1.05)	1.01 (0.96 to 1.06)
≥9 cGy	0.90 (0.73 to 1.10)	0.99 (0.81 to 1.22)	0.97 (0.91 to 1.03)
ERR per unit of risk predicted from studies of external exposure (95% CI)†	0.04 (<0 to 0.32)	0.10 (−0.16 to 0.46)	−0.02 (−0.09 to 0.04)
P‡	.74	.48	.46
Relative risks by categories of predicted risk (95% CI)†			
0.0–0.299§	1.00	1.00	1.00
0.3–0.599	1.01 (0.84 to 1.22)	1.07 (0.88 to 1.30)	1.01 (0.95 to 1.08)
≥0.6	1.24 (0.99 to 1.55)	1.29 (1.01 to 1.64)	0.96 (0.90 to 1.03)

*For comparability with high-dose studies, estimates are presented per Gy even though none of the doses in this study were as high as 1 Gy.

†CI = confidence interval.

‡Two-sided P value based on likelihood ratio chi-squared test for linear trend.

§Reference category.

Table 3. Estimates of the excess relative risk (ERR) per Gray (Gy)* of ^{131}I dose by age at exposure

Analysis, age at exposure	Mortality data: County-specific doses ERR per Gy (95% CI)†	Mortality data: County-specific doses P‡	Mortality data: State-specific doses ERR per Gy (95% CI)†	Mortality data: State-specific doses P‡	Incidence data: county-specific doses ERR per Gy (95% CI)†	Incidence data: county-specific doses P‡
A, <1 y	10.6 (−1.1 to 29)	.085	16.6 (−0.2 to 43)	.054	2.4 (−0.5 to 5.6)	.11
B, <5 y	1.5 (<0 to 5.7)	.35	2.7 (−1.1 to 8.4)	.19	−0.1 (−0.8 to 0.8)	.89
C, <15 y	−0.2 (<0 to 1.6)	.79	0.1 (−1.6 to 2.3)	.92	−0.3 (−0.8 to 0.2)	.22
D§						
<1 y	13 (−1.2 to 31)		22 (−2.5 to 53)		6.6 (2.5 to 11)	
1–5 y	−1.2 (<0 to 3.7)	.17‖	−2.3 (<0 to 5.9)	.13‖	−2.2 (−3.3 to −0.7)	.004‖
E§						
<1 y	13 (0.8 to 32)		22 (3.2 to 50)		5.1 (1.7 to 8.8)	
1–15 y	−1.0 (<0 to 0.6)	.087‖	−1.6 (<0 to 0.8)	.062‖	−1.0 (−1.5 to −0.4)	.003‖

*For comparability with high-dose studies, estimates are presented per Gy even though none of the doses in this study were as high as 1 Gy.

†CI = confidence interval.

‡Two-sided P value based on likelihood ratio chi-squared test for linear trend.

§These analyses simultaneously estimated risks for two age-at-exposure variables.

‖These P values are based on 2 degrees of freedom and test the null hypothesis of no effect.

Washington County; without the 9+ cGy data, the estimated ERR was reduced from 2.4 to 1.5 per Gy, and the *P* value changed from .11 to .33. For the mortality analyses based on state-specific doses, there were no data with doses under age 1 year exceeding 9 cGy, and results did not seem to be strongly influenced by a small number of deaths in subjects with relatively high doses.

Analyses including only dose received under age 5 years (analysis B in Table 3) or only dose received under age 15 years (analysis C in Table 3) provided little evidence of a dose–response relationship. For analyses that included doses received at two different ages (analyses D and E in Table 3), estimated ERRs for dose received under age 1 year were positive, whereas estimates for contributions at other ages were negative. For the incidence data, the upper confidence limits for the ERRs for doses received at ages older than 1 year were negative.

Table 4 shows results for specific birth cohorts. The mortality data, but not the incidence data, indicate a significant dose–response relationship for both the county- and state-specific doses in the 1955 cohort. When mortality analyses were limited to the counties and time period covered by the incidence data, evidence of a dose–response relationship was still found for the 1955 cohort, even though only 12 thyroid cancer deaths occurred in this group. Largely because of the 1955 cohort results, statistically significant heterogeneity among the five cohorts was found. Heterogeneity among birth cohorts was also found for the risk-weighted dose with the mortality data.

One of the distinctions of the 1955 birth cohort is that a substantial proportion of the dose would have been received under 1 year of age. There was no dose received under 1 year of age for the two earliest cohorts, and there was very little dose received at any age for the latest cohort. On the basis of the county-specific mortality data, it was found that the estimated ERR per Gy for dose received under age 1 year in the 1955 cohort was 46 (95% CI = 12 to 123), whereas the comparable estimate for the 1950 cohort was −2.8 (95% CI = <0 to 14), a difference that is statistically significant ($P = .008$). For the 1955 cohort, all of the age-specific dose measures evaluated in Table 3 yielded positive ERR estimates, including dose for age 1–5 years and dose for age 1–15 years as in analyses D and E, respectively. The strongest evidence of risk was for dose received under age 1 year ($P = .0015$), and the addition of dose for older age categories (1–5 years or 1–15 years) as in analyses D and E resulted in only negligible improvements in fit ($P>.50$).

Sex-specific analyses were also conducted. With the county-specific mortality data, the ERRs per Gy were very similar for the two sexes; however, with the incidence data, the ERRs for the two sexes differed ($P = .051$), although both were negative. The estimated ERRs for dose received under age 1 year were not statistically significantly different by sex for either the mortality or the incidence data.

Discussion

No association was found for either thyroid cancer mortality or incidence with cumulative ^{131}I dose, risk-weighted dose, or dose received after 1 year of age in the entire cohort. However, both incidence and mortality rates were found to be associated with ^{131}I dose received under 1 year of age, and thyroid cancer mortality

Table 4. Estimates of the excess relative risk (ERR) per Gray (Gy)* of ^{131}I dose by birth cohort, and estimates of relative risk (RR) by categories of dose for the 1955 birth cohort

	Mortality data					
	County-specific doses†		State-specific doses†		Incidence data: county-specific doses‡	
Birth cohort	ERR per Gy (95% CI)§	*P*‖	ERR per Gy (95% CI)§	*P*‖	ERR per Gy (95% CI)§	*P*‖
1940 and earlier	−1.7 (<0 to 0.9)	.17	−0.6 (−3.4 to 2.7)	.69	−0.9 (−2.2 to 0.7)	.25
1945	−1.1 (<0 to 0.6)	.13	−2.5 (<0 to 0.7)	.11	−0.8 (−1.6 to 0.2)	.13
1950	−0.2 (<0 to 2.8)	.90	0.0 (−2.1 to 3.5)	.98	−0.5 (−1.1 to 0.2)	.14
1955	12.0 (2.8 to 31)	.003	13.2 (2.7 to 36)	.005	0.3 (−0.7 to 1.4)	.60
1960 and later	−1.0 (<0 to 14)	.86	0.8 (<0 to 24)	.92	0.8 (−1.1 to 2.9)	.43
P value‖ for homogeneity based on chi-square with 4 degrees of freedom	.015		.033		.37	

	Mortality data					
	County-specific doses†		State-specific doses†		Incidence data: county-specific doses‡	
1955 birth cohort by dose	RR (95% CI)§	No. of deaths	RR (95% CI)§	No. of deaths	RR (95% CI)§	No. of cases
0–3.99 cGy¶	1.00	57	1.00	52	1.00	1124
4–8.99 cGy	1.58 (1.06 to 2.35)	52	1.42 (0.95 to 2.12)	53	1.01 (0.90 to 1.13)	472
≥9 cGy	1.68 (1.00 to 2.80)	23	2.00 (1.19 to 3.36)	27	1.09 (0.95 to 1.23)	308

*For comparability with high-dose studies, estimates are presented per Gy even though none of the doses in this study were as high as 1 Gy.

†The numbers of deaths included in the mortality analyses were 3805, 328, 212, 132, and 125 for the respective birth cohorts 1940 and earlier, 1945, 1950, 1955, and 1960 and later.

‡The numbers of cases included in the incidence analyses were 3862, 1928, 2076, 1904, and 2887 for the respective birth cohorts 1940 and earlier, 1945, 1950, 1955, and 1960 and later.

§CI = confidence interval.

‖Two-sided *P* value based on likelihood ratio chi-squared test for linear trend.

¶Reference category.

rates were found to be associated with lifetime dose for the 1955 birth cohort. To evaluate whether these latter associations reflect causal relationships, we will first discuss the limitations and biases in this study and then briefly review the relevant literature on the relationship between exposure to ^{131}I and thyroid cancer risk, with particular attention to the dependence of risk on age at exposure.

Limitations and Biases

The ecologic approach used in this report is subject to many limitations *(6–8)*. A particular problem in our analyses is that dose estimates are subject to large uncertainties, which can be expected to distort results in various ways *(7–9)*. A major source of error is migration. In the years 1940–1980, nearly 20% of the U.S. population changed their county of residence in any given 5-year period, with about half also changing their state of residence *(10)*. In a mobile society, many persons are diagnosed with thyroid cancer or die of thyroid cancer in different counties (or states) from those in which they were exposed in the 1950s and, thus, have incorrect doses assigned to them. This situation would be expected to dilute radiation effects that might have occurred.

Further uncertainties in dose estimates are discussed in detail in the NCI report *(1)*. In brief, the most important factor that distinguishes doses among geographic areas is the estimated amount of deposited radioactive material. For tests conducted in the period 1951–1958, deposition estimates were based on historical monitoring data. The number of monitoring stations varied with time but never exceeded 100; thus, there is considerable uncertainty in using these data to estimate depositions for more than 3000 counties.

Doses depend strongly on patterns of milk consumption. For persons exposed in infancy (ages 0–1 year), doses depend on the source of milk (i.e., formula, mother's milk, or fresh cow's milk) rather than on the milk consumption rate, which does not vary much in this age category. For older children, the rate of milk consumption is an important factor; e.g., a child between the ages of 1 and 5 years who drinks no milk would receive a dose to the thyroid that is only about one-tenth that of a child who drinks an average amount of milk. Milk consumption varies widely, and the average doses used in our analyses do not capture this variability. Furthermore, even average doses could be estimated inaccurately if the milk consumption distributions used to determine average county doses were not correct. Further variability and uncertainty result from inaccuracies in estimating milk sources, the interval between milking the cow and drinking the milk, the amount of pasture grass consumed daily by cows, the fraction of ^{131}I intake by cows that finds its way into milk, and many other factors.

Another limitation of the approach taken in these analyses is that thyroid cancer incidence and mortality rates may depend on geographic-, time-, or cohort-related factors other than dose received from the nuclear tests in the 1950s. Incidence rates of thyroid cancer are highly dependent on the frequency, intensity, and methods of clinical evaluation of the thyroid *(11,12)*, all of which vary with time and location. Because external medical irradiation was common in the United States in the 1940s and 1950s, many thyroid cancer-screening programs were initiated starting about 1974, but the screening methods differed *(13)*. With the exception of special screening conducted for an epidemiologic study of persons exposed in three counties in Utah, Nevada, and Arizona (*see* next section), it is unlikely that screening was more intensive for persons exposed to larger doses from fallout, since the geographic pattern of these doses was not widely known until recently. Stratifying on age, birth year, and sex and emphasizing those age–calendar year combinations that included persons who were young in the 1950s should have reduced bias from confounding but cannot be counted on to eliminate it.

Relevant Literature on Effects of ^{131}I Exposure

Many studies have demonstrated that exposure to external (x-ray or gamma) radiation can induce thyroid cancer even at doses as low as 10 cGy *(11)*. Ron et al. *(4)* obtained an estimated ERR of 7.7 per Gy (95% CI = 2.1 to 29) from a combined analysis of five cohorts exposed under the age of 15 years. They also showed that risk (ERR per Gy) decreases with age at exposure, that there is little evidence of risk from exposure in adulthood, that the dose–response relationship is compatible with linearity, and that fractionated exposure might be slightly less carcinogenic than acute exposure. These studies do not support risks limited to exposure in infancy.

Exposure to ^{131}I differs from external exposure in that the dose to the thyroid is gradually absorbed over several weeks and the dose distribution within the gland is not uniform. Exposure to ^{131}I has been demonstrated to induce thyroid cancer in experimental animals, but most early experiments on rodents exposed to high doses found risks that were lower than risks associated with external radiation exposure *(14)*. However, a later large and well-conducted study *(15)* in rats found that, for doses lower than 400 cGy, the risk of thyroid cancer associated with ^{131}I exposure was comparable to the risk associated with external exposure. In that study *(15)*, all rats were exposed at 6 weeks of age, which would correspond to about 3 years of age in humans if expressed as a fraction of total lifespan. The 1985 recommendation of the National Council on Radiation Protection and Measurements *(14)* that risk estimates for ^{131}I exposure be based on the assumption that the ratio of risks from ^{131}I and external exposure is 0.3 is being re-evaluated.

Studies of persons exposed to ^{131}I for diagnostic or therapeutic reasons have included very few persons exposed under the age of 20 years and have yielded conflicting results *(16–19)*. Marshall Islanders exposed to radioactive fallout from a nuclear weapons test in 1954 clearly experienced an excess of thyroid cancer, but the dose received by these persons was mainly from short-lived radioisotopes and gamma radiation rather than from ^{131}I *(20,21)*.

Persons exposed as children to ^{131}I in southwestern Utah, southeastern Nevada, and southeastern Arizona from nuclear tests in Nevada have also been studied *(22,23)*. Eight thyroid cancers were found in 2500 subjects, and risk was associated with dose. Although based on small numbers of subjects and not statistically significant, the association became statistically significant when malignant and benign neoplasms were combined.

Large increases in thyroid cancer incidence have been observed in Belarus, Ukraine, and Russia among persons who were exposed to ^{131}I when under 20 years of age as a result of the Chernobyl acci-

dent in 1986 *(24–26)*. Current data indicate that these increases in risk are related to exposures from radioiodines (including ^{131}I) and cannot be explained entirely by the thyroid screening that has been conducted in the affected areas *(27,28)*. Many of these subjects had doses to the thyroid that exceeded 30 cGy, larger than most doses received from fallout in the United States *(28)*. Quantitative risk estimates and modifying effects of age at exposure have not been reported.

Findings and Interpretation

Although quantification of thyroid cancer risks from ^{131}I exposure remains highly uncertain, the clear demonstration of risk from external exposure in humans and from ^{131}I exposure in animals, together with the emerging evidence in humans from the Chernobyl experience, provides evidence that exposure to ^{131}I can induce human thyroid cancer. For this reason, it seems likely that exposures to the U.S. general public from atmospheric nuclear tests conducted in Nevada in the 1950s caused some excess thyroid cancers.

An association limited to dose received under age 1 year was not of course an *a priori* hypothesis. Because an association was found in both the mortality and the incidence data, this finding cannot be readily dismissed as attributable to chance, although the association does not necessarily imply causality. The types of disease contributing to thyroid cancer mortality and incidence rates differ considerably, with mortality data showing a fairly equal balance of males and females and a high proportion of undifferentiated carcinomas and the incidence data showing a predominance of females with papillary or follicular cancers *(11)*.

The mortality finding for dose received under age 1 year was fragile in that it was strongly influenced by two deaths. The incidence finding depended on results from Washington County, UT, where it is known that special screening was conducted for an epidemiologic study *(22,23)*. The special screening cannot account for all nine cases in our study, since only five thyroid cancers were detected during the Utah screening *(23)*; furthermore, seven of the nine cancers in our study were diagnosed in the years 1987–1992, later than the 1985–1986 period of screening. Nevertheless, Washington County was clearly subject to heightened awareness of thyroid cancer. Among the counties included in our incidence analyses, the highest doses were found in four Utah counties (Washington, Garfield, Kane, and Millard), and high rates of thyroid cancer were observed only in Washington County.

In addition, the restriction of risk to exposure under 1 year of age is not compatible with the strong evidence of risk from external exposure to radiation between the ages of 1 year and 15 years *(4)*. Differences in the nature of dose-estimation errors for different ages at exposure might have played a role. For older children, variability in rates of milk consumption is an important factor; in contrast, for infants, variability in the sources of milk is probably more important. It is possible (although the mechanism is not clear) that the latter variability has distorted results less than the former. It is also possible that the age-dependence pattern for risks from exposure to ^{131}I is different from that for risks from external exposure.

The association identified for the mortality data in the 1955 birth cohort largely reflects the association for dose received under age 1 year, since approximately 84% of this cohort would have received such a dose and since adding doses received at older ages to a model with dose received under age 1 year did not result in statistically significant improvements in the model fit. The differences between the 1950 and 1955 birth cohorts are difficult to explain. Although only about 18% of the 1950 cohort would have received a dose under 1 year of age, the ERR per Gy for this dose differed significantly from that in the 1955 cohort. No evidence of such heterogeneity was found for the incidence data.

The quantitative estimates obtained from our study were often negative, and many of the upper confidence limits were lower than those reported from studies of persons exposed to external radiation. For example, the estimated ERR reported by Ron et al. *(4)* for subjects exposed under the age of 15 years was 7.7 per Gy, which is larger than any of the upper confidence limits shown for such exposure in analysis C of Table 3. Also, the upper confidence limits for the risk-based dose (Table 2), expressed as multiples of the risk predicted from external exposure studies, are all less than 1.0. Even for dose received under age 1 year or for the 1955 cohort, risk estimates do not greatly exceed those based on studies of external exposure. Such comparisons should be interpreted with caution because errors in dose estimation have almost certainly led to underestimation of risk in our study.

It is possible that exposure to ^{131}I in the 1950s contributed to the increase in risk of thyroid cancer, both with increasing dose received under age 1 year and, for the mortality data, with increasing total dose for those born in the mid-1950s. The fact that similar increases were not observed for doses received at ages greater than 1 year or among those born slightly earlier is not compatible with evidence from populations exposed to external radiation during childhood. However, this discrepancy might be explained by the many limitations and biases inherent in ecologic studies, especially those resulting from migration and other errors in dose estimates that are likely to have greatly diluted the estimated relationship between thyroid cancer risk and ^{131}I dose. While these limitations preclude meaningful quantitative estimates of risk, it is perhaps remarkable that any evidence of effects of ^{131}I exposure emerges from our ecologic study. Further studies of animals exposed early in life or of human populations, such as children exposed as a result of the Chernobyl accident, may allow more precise quantification of risks from exposure to ^{131}I.

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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